Postpartum hemorrhage detection and treatment care pathways and identifying interventions: A decision tree model

Christopher Troeger

Program Officer, Statistics and Modeling
Maternal, Newborn, and Child Health Discovery & Tools
Bill and Melinda Gates Foundation
chris.troeger@gatesfoundation.org
Background

- **Postpartum hemorrhage (PPH)** is one of the leading causes of maternal mortality and morbidity.
- The majority of PPH deaths occur in South Asia and sub-Saharan Africa (35,000-65,000 deaths).
- Almost half of women with clinical postpartum hemorrhage are not diagnosed or do not receive the standard of care uterotonics.

Results from GBD 2019

Postpartum hemorrhage deaths per 100,000 in 2019

Postpartum blood loss and treatment with uterotonics

Evidence from the multicenter WHO CHAMPION study
Motivation and Goals

• We built a decision tree model to better understand when and where in a diagnostic and treatment cascade women are suffering and dying from PPH in South Asia and sub-Saharan Africa
  • How is PPH burden distributed by birth location?
  • How is PPH burden distributed among detected/undetected or treated/untreated quality-of-care indicators?
• The model is also built to evaluate intervention impact potential
  • What fraction of PPH burden is prevented? Treated?
  • What is the residual burden after the avertable fraction?
• These results may provide insights into the types of policies or interventions that would reduce this burden of disease
Methods: Overview

- This model is a deterministic decision tree where pregnant women in South Asia and sub-Saharan Africa are segmented into PPH outcomes depending on underlying risk, location of delivery, and diagnostic and treatment coverage.
- Outputs include deaths, moderate and severe episodes, years lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life-years (DALYs) lost at many steps of the PPH incidence and treatment pathway.

* Treated* = 1st response bundle followed by additional measures (e.g., removal of repaired tissue) as needed if in high-level facility.

Assume differential rates of success/failure by facility level.

*PPH ? Yes
  * Detected? Yes
    * Referral / Treated? Yes
      * Referred
      * Treated*
      * Survival with disability
      * Death
    * Detected
      * PPH
    * PPH
  * Detected
    * PPH
  * Detected
    * PPH
  * PPH

*PPH ? Yes
  * Detected? Yes
    * Referral / Treated? Yes
      * Referred
      * Treated*
      * Survival with disability
      * Death
    * Detected
      * PPH
    * PPH
  * Detected
    * PPH
  * Detected
    * PPH
  * PPH
Methods: Input data

Input data from several sources

- Burden (incidence, deaths, disability) and demographics (pregnancies, live births): Global Burden of Disease Study 2019 (GBD)
  - The model is calibrated to match estimates of PPH morbidity and mortality from the GBD (*Supplemental slides*)
- Risk factors and relative risks: Pooled analyses, systematic reviews (*Supplemental slides*)
  - Anemia (35-50% of pregnant women; RR of about 2.7)
  - Home birth (about 30% of births; incidence RR 1.82, mortality RR 4.5)
  - Caesarean Section delivery (5-20% of births; RR 1.85)
- Interventions: **E-MOTIVE (early detection and treatment)***, iron for anemia, other novel interventions
- Uncertainty in input data from published reviews or statistical analyses
- Randomness constructed from draws from distributions of input parameters (*Supplemental slides*)

*Gallos et al. NEJM, May 2023*
Methods: Forecasts

- We used existing forecasts of live births and the socio-demographic index (SDI) from the Institute for Health Metrics and Evaluation through the year 2040.
- The SDI forecasts were used to make predictions of anemia prevalence, in-facility delivery, and Caesarean-section delivery at the country-level and then aggregated to the regional level (South Asia & sub-Saharan Africa).
- Baseline incidence and mortality rates are calibrated to GBD 2019 estimates and we assume changes in PPH outcomes are driven by other parameters in the model including anemia, in-facility delivery, Caesarean-section, live births, and intervention coverage.
Interventions: Early detection and case management (E-MOTIVE)

- Early detection and management is crucial for preventing severe episodes and deaths yet almost half of all clinical PPH episodes were not treated with the first-line uterotonic (oxytocin).

- Scale-up of the E-MOTIVE bundle (Early detection, Massage of the uterus, Oxytocin, Tranexamic acid, IV fluids, and Examination/Escalation). This bundle was very effective in preventing severe PPH in low-income settings (Relative risk 0.4, 0.32-0.50)*
  - Diagnostic sensitivity of PPH higher in intervention group (93.1%) compared to control group (51.1%) based on objective measurement of blood loss.
  - Compliance with MOTIVE bundle higher in intervention group (91.2%) compared to control group (19.4%).
  - Our model considers a scale-up in detection and treatment of PPH following these study results.

*Gallos et al. NEJM, May 2023
Results: Baseline in 2019

- Postpartum hemorrhage is not diagnosed in about 57% of cases and 77.7% of deaths. These women do not receive standard of care including uterotonics (oxytocin), tranexamic acid, or uterine massage.

- Deaths are concentrated in home births: about a third of episodes occurred in home births but four-fifths of deaths occurred in home births

Figures show the percent and number of postpartum hemorrhage deaths at different levels of care cascade.
Results: E-MOTIVE bundle counterfactual in 2019

- The E-MOTIVE bundle
  - Increases PPH detection in-facility from about 50 to 90%
  - Increases MOTIVE treatment in-facility from about 20-90%
  - Results in about 1,901,000 more episodes diagnosed and treated (95% CI 1,378,000-2,543,000)
  - Results in 4,380 fewer deaths in 2019 (95% CI 2,800-5,800)
  - Shift in residual deaths due to higher detection but imperfect treatment results in slight increase in deaths occurring after failed standard of care treatment and after failed emergency measures
  - Residual deaths are overwhelmingly home births (91.4%)
Results: Forecasts of drivers of postpartum hemorrhage

- **Live births**: Graphs showing the trend of live births over time in South Asia and Sub-Saharan Africa.
- **C-section delivery**: Graphs showing the proportion of C-section deliveries as a fraction of inpatient deliveries in South Asia and Sub-Saharan Africa.
- **In-facility delivery**: Graphs showing the proportion of in-facility deliveries in South Asia and Sub-Saharan Africa.
- **Moderate/Severe anemia**: Graphs showing the proportion of moderate and severe anemia in South Asia and Sub-Saharan Africa.

Forecast: No ↔ Yes
Results: Forecasting postpartum hemorrhage to 2040

- Projected trends in live births, anemia prevalence, C-section delivery, and in-facility delivery suggest a decline in deaths from 44,500 in 2019 to 26,300 in 2040
Results: Scale-up E-MOTIVE bundle to 2040

- Scale-up of E-MOTIVE bundle to 90% by 2040 accelerates these trends, averting a cumulative 49,000 deaths (95% CI 32,700-65,000) and 2,253,000 DALYs (95% CI 1,389,000-3,099,000) through 2040.
Increasing coverage of E-MOTIVE also changes the residual addressable burden.

The fraction of deaths that are detected but unresolved by treatment increases from 15.3% in 2019 to 47.2% in the E-MOTIVE scale-up.

This is because imperfect effectiveness of treatment results in more detected but unsuccessfully treated episodes.
Interpretation:

- Most postpartum hemorrhage episodes and deaths are never diagnosed and do not receive standard of care including uterotonics, tranexamic acid, uterine massage, or IV fluids (MOTIVE bundle).
- Most postpartum hemorrhage deaths occur in births outside of facilities and this fraction is likely to increase as in-facility detection and treatment improves.
- The E-MOTIVE intervention to identify, treat with standard of care, and escalate postpartum hemorrhage episodes could avert 10% of deaths in South Asia and sub-Saharan Africa in 2019 and 50,000 cumulative deaths through 2040.
- As more episodes are identified, novel strategies or interventions to treat postpartum hemorrhage are probably required for the residual burden that is not averted with E-MOTIVE.
- This segmentation model can be used to understand where and when women suffer from postpartum hemorrhage disability and mortality and to assess potential impact of other interventions.
Next steps:

- Refining impact model to test additional counterfactual scenarios
  - Modify risk factors for postpartum hemorrhage including intravenous iron for anemia and AI-enabled ultrasound to support risk-differentiated referral
- Consider strategies to address large residual burden in home births
- More robust estimation of non-fatal disease burden
Thank you and acknowledgements

Thank you to Laura Lamberti and to the MNCH D&T team for support and expertise!

Questions?

Christopher Troeger
Program Officer, Statistics and Modeling
Maternal, Newborn, and Child Health Diagnostics and Tools
Bill and Melinda Gates Foundation
chris.troeger@gatesfoundation.org
Input values for PPH death envelope

- Counts from the Global Burden of Disease study 2019
- Deaths in Nigeria very different between GBD and MMEIG, so:
  - Substitute PPH deaths in Nigeria from GBD with deaths based on MMR from 2018 DHS using the same post-partum cause fraction (~28%; from GBD)
    - \[512 \times \text{live births} / 100,000 \times 0.282\]
  - Resulting maternal deaths in Nigeria between GBD & MMEIG estimates
  - Increases PPH deaths in SA & SSA from about 38,400 to 44,500

<table>
<thead>
<tr>
<th>Analysis of death estimates from different sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live births (comparison analysis)</strong></td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>GBD</strong></td>
</tr>
<tr>
<td>South Asia</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>Nigeria</td>
</tr>
<tr>
<td>Total SA &amp; SSA</td>
</tr>
<tr>
<td><strong>MMEIG</strong></td>
</tr>
<tr>
<td>South Asia</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>Nigeria</td>
</tr>
<tr>
<td>Total SA &amp; SSA</td>
</tr>
<tr>
<td><strong>Birmingham</strong></td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>South Asia</td>
</tr>
<tr>
<td><strong>DHS</strong></td>
</tr>
<tr>
<td>Nigeria</td>
</tr>
</tbody>
</table>

Replacing GBD Nigeria with DHS

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria</td>
<td>22,970.70</td>
<td></td>
<td>44,476.70</td>
</tr>
</tbody>
</table>
Relative risk of PPH incidence given C-section delivery (1.85, 95% CI 1.7, 2.0) [Postpartum Hemorrhage Summit, 2023]

- Prevalence of C-section delivery from GBD 2021

Relative risk of PPH incidence in home birth compared to facility delivery (1.82, 95% CI 1.07-2.61) [Calvert et al. 2012]

Relative risk of PPH death in non-facility to facility delivery (4.5, 95% CI 4.0-5.0) [Calvert et al. 2012]

- In-facility delivery percent from GBD 2019
- Split between high-level and low-level facilities from analysis of CLIP study

Relative risk of PPH given moderate/severe anemia compared to not anemic (2.70, 95% CI 2.0-3.65) [Next slide]

- Anemia prevalence among women 15-49 from GBD 2019
ODDS OF POST PARTUM HEMORRHAGE GIVEN ANEMIA

Uses results from two systematic reviews, supplemented with primary data from MOMI, PRISMA, and WOMAN-2 trials

Moderate/Severe: 2.70 (2.0-3.65)
Any: 1.49 (1.03-2.16)
The primary results of a randomized study evaluating the effectiveness of the EMOTIVE bundle was published in May 2023 in NEJM.

Study was multi-country, cluster-randomized trial to assess risk of severe PPH, laparotomy, or maternal death due to bleeding in clusters that received the intervention compared to those that didn’t.

Kenya, Nigeria, South Africa, Tanzania (80 hospitals)
Supplementary slides: Uncertainty in input parameters

- Four or more ANC visits
- Prevalence of Caesarean section delivery in South Asia
- Prevalence of Caesarean section delivery in sub-Saharan Africa
- In-facility delivery (any)
- High-level facility delivery
- Prevalence ratio of home births with ultrasound in 32-38 weeks to all births
- Low-level facility delivery
Supplementary slides: Uncertainty in input parameters
Supplementary slides: Uncertainty in input parameters

- Coverage of eMOTIVE bundle
- Coverage of tranexamic acid outside of eMOTIVE
- Fraction women with PPH that receive any uterotonics
- Efficacy of emergency response
- Efficacy of IV iron from mod/severe anemia to none/mild
- RR of tranexamic acid on mortality
- Population within 2 hours of comprehensive emergency obstetric care (CEmOC)
- Efficacy of eMOTIVE bundle on primary endpoints
- Home delivery receiving IV iron
- Fraction of eMOTIVE and uterotonic efficacy at low-level facilities
- Frequency of detection of PPH at home
- Receives IV iron
- Successful referral from low to high-level
- Proportion of women with risk for PPH identified through ultrasound
- Proportion receiving ultrasound in third trimester
- Efficacy of uterotonic on severe PPH